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Review Article

Neuroimmunoendocrine System in Health and Disease

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Abstract

Various stressors activate the hypothalamo-pituitary-adrenal axis (HPA-axis) that stimulates adrenal secretion of glucocorticoids, thereby playing critical roles in the modulation of immune responses. Transcriptional regulation of nuclear genes has been well documented to underlie the mechanism of glucocorticoid dependent modulation of cytokine production and immune reactions. Recent advances in understanding the complex interconnections between inflammatory signals and various hormones have been defined as a "double-way street". There is a critical balance between hormones such as prolactin, glucocorticoids, catecholamines, pro-inflammatory cytokines and endocrine organs with the nervous system, which are called "white tissues". Such balance under certain circumstances may influence the immune response of the host and consequently determine the course of an infection of a disease during an inflammatory state. This review aims to show some of the pathways that drive bi-directional communication between immune, nervous and endocrine system, with emphasis on pro-inflammatory cytokines and various immunomodulatory hormones such as glucocorticoids.

Keywords: *Adrenal Hypothalamic Pituitary Axis; Immune System; Cytokines; Glucocorticoids*

Introduction

Multiple evidences indicate that there is a bidirectional communication between the neuroendocrine and immune system. This communication is constantly evidenced under stress situations such as infections, inflammatory/autoimmune diseases or trauma, which trigger a series of reactions that activate the neuroimmunoendocrine system [1,2].

The neuroimmunoendocrine system is composed of the following axis: 1) hypothalamic-pituitary-adrenal axis (HPA), 2) hypothalamic-pituitary-gonadal axis (HHG), 3) hypothalamic-pituitary-thyroid axis (HHT) and 4) prolactin/hormone system of growth (PRL / GH) [3,4].

The messengers of this bidirectional communication are hormones, neuropeptides, pro-inflammatory and anti-inflammatory cytokines, and neurotransmitters that are synthesized by the cells of the all axis. These messengers act via receptors, producing activation or inhibition of the innate and adaptive immune response, as well as in the nervous and endocrine system [5]. The autonomic nervous system and the synthesis and release of catecholamines also participate in said communication [2]. The synthesis and release of the messengers has cycles of 24 hours of action on the physiological processes. These variations are called circadian rhythm, which is generated and controlled by the central nervous system through the hypothalamus [6].

Stress is defined as a response to various stressors that include hazardous chemicals, pathogens, and psychological events. Various stressors activate the hypothalamo-pituitary-adrenal axis (HPA-axis) to maintain a wide variety of homeostatic processes including immune responses. When exposed to stressors, HPA axis stimulated adrenal secretion of glucocorticoid modulates immunological reactions by regulating the transcription of nuclear genes encoding various cytokines and inflammation-related proteins. It has been well documented that strong stress suppresses innate immune reactions against a variety of pathogens, though its precise mechanism remains obscure. Hyper-activation of the HPA-axis and dysregulation of the neuro-endocrine network have been reported to underlie the pathogenesis of stress-induced emotional disorders, such as anxiety, anorexia nervosa and depression, and down-regulation of the host defense system against bacterial infection [7,8].

Responses to stressors play critical roles in the maintenance of homeostasis in animals, aiding their survival by adapting to their environments. Stimulation of the HPA axis and sympathetic adrenal medullary axis through neuronal networks enhances the secretion of glucocorticoids and catecholamine, an adrenergic neurotransmitter. The neuroendocrine system plays important roles in the regulation of stress induced biological reactions including digestion of food, energy metabolism, immune systems, and control of emotion. Neuroendocrinological regulation of immune responses is essential for the survival of a host suffering from infection and inflammatory diseases and glucocorticoids released by HPA-axis-dependent mechanisms plays critical roles in the regulation of immune systems [9].

In response to various stressors, corticotropin-releasing factor (CRF) is released from the hypothalamus into the hypophysial portal vein to stimulate the anterior pituitary gland, thereby releasing adrenocorticotropic hormone (ACTH) into the systemic circulation. ACTH in the circulation binds to the type-2 melanocortin receptor (MC2R) in the adrenal cortex, where it stimulates the synthesis and release of glucocorticoids into the circulation [10]. Glucocorticoids secreted into the circulation inhibit further activation of the HPA-axis through the glucocorticoid receptor (GR)-mediated feedback mechanism in the brain, to regulate homeostasis of stress related hormones.

Bidirectional Communication between Immune and Neuroendocrine Systems

The nervous system can communicate with the immune system through two main routes: the neuroendocrine axis and the autonomic nervous system. The sympathetic and parasympathetic neural pathway regulates the innate immune response at regional, local and systemic level, through neurotransmitters and neuropeptides, intestinal vasoactive peptide (VIP), substance P (SP) and peptides related to calcitonin gene [9,10], which; they act directly on receptors located on the membrane of other neurons or on various types of target cells [11].

Many cytokines can be secreted by cells of the Central Nervous System at several brain sites, with IFN-α, IFN-γ, IL-1, IL-2, IL-6 and TNF-α produced by astrocytes and microglia. In the hypothalamus and pituitary gland, IL-1, IL-6, TGF-β, IL-10 and IL-18 [12,13] are secreted. However, the main cytokines involved in the immune-nervous system communication (SI-SN) are: IL-1, TNF-α, IL-2, IL-6, IFN-γ, IL-12 and IL-10 [14].

IL-2, a proliferative cytokine produced by several cells of the immune system including T helper cells of the Th1 pattern, exerts effects on neuroendocrine cells and neurons [15], stimulating the production of the adrenocorticotropic hormone (ACTH) by the cells of the adenohypophysis [5]. Likewise, in rats IL-1 increases plasma concentrations of ACTH and stimulates the release of GH, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in adenohypophyseal cells [15], while IL-6 induces synthesis of hepcidin (HAMP) during inflammation through the activation of STAT3 [16].

Diverse hormones and their receptors have been identified in tissues and cells associated with the immune system and have been shown to participate in the development, differentiation and regulation of the immune response during lymphocyte activation mediated by the presence of antigens, probably acting in an autocrine form/paracrine [17,18]. On the other hand, it has been proven that lymphocytes are capable of producing hormones such as GH, PRL, adrenocorticotropic hormone (or ACTH), thyroid stimulating hormone (TSH), insulin growth factor (IGF-1), leptin and gonadotropins [19]. *In vivo* studies, such as *in vitro*, have also reported the expression of HAMP in neutrophils and macrophages [20], as well as in lymphocytes of fish and humans [21].

Thus, neurotransmitters, neuropeptides, cytokines and hormones interact with receptors located in the cells of both CNS and SI systems, allowing the CNS to detect alterations in the immune activity through a molecular sensory system; after which a change in the immune response begins in the presence of conditioned stimuli [10].

The cells of the immune system in their resting state or after activation express on their surface receptors for hormones and peptides. Similarly, cells of the nervous and endocrine systems express receptors for various cytokines, chemokines, and growth factors. The interactions between these systems are critical for the maintenance of a homeostatic balance within the organism and alterations in them in response to disease, stress, injuries and/or metabolic alterations can cause significant changes in the immune response and susceptibility to infections and autoimmune diseases.

During the course of an infectious disease, the host generates local and systemic defense mechanisms that include the secretion of various cytokines that generate not only an innate and adaptive immune response, but also significant endocrine effects that in turn lead to important changes in immunological, metabolic, endocrine and neural function [22]. The immune response to a specific pathogen includes the inflammatory process which has an altered hormonal response. For example, immunity to intracellular pathogens such as protozoa and mycobacteria is mediated by IFN-γ, TNF-α and IL-1 that activate the microbicidal capacity of macrophages. Such cytokines stimulate the HPA axis by increasing the serum levels of glucocorticoids (GC) and other adrenal steroids such as dehydroepiandrosterone (DHEA) [23].

Due to these evidences, neuro-immuno-endocrine interactions have begun to be considered as a new protagonist in the regulation of infections, including parasitic infections. A clear example is the hormones derived from the hypothalamic-pituitary-adrenal axis (HPA), which affect the parasite-host relationship through its direct effects on *Schistosoma mansoni* inhibiting its proliferation, or through indirect effects modulating the immune response of the host [24].

The HPA axis plays a key role in the response to stress. The corticotropin-releasing factor (CRH), adrenocorticotropin (ACTH) and glucocorticoids, through the activation of the stress response, the modulation of pro-inflammatory cytokines and the regulation of the peripheral immune response mediate control of neuroimmunoendocrine interactions [25]. Thus, the function of the HPA axis can be considered as a target in human and experimental Chagas disease.

Chagas disease or American trypanosomiasis is a zoonosis caused by the flagellated protozoan *Trypanosoma cruzi* and is recognized by the World Health Organization as one of the 13 neglected tropical diseases that affects between 8 to 10 million people around the world, mainly in Latin America where the disease is endemic. It is considered the parasitic infection with the greatest economic burden in Latin America due to its prolonged chronicity [26,27]. However, there is a passive attitude caused by the ignorance of the magnitude of the disease in terms of case detection, which diminishes the perception of its true impact, reinforces the idea of a silenced, forgotten disease that leads to an underestimation for the design and development of rational drugs.

In acutely infected individuals, parasites can be found in both nervous and endocrine tissues, and in the immune system, including the thymus [28-33], and promote an neuroimmunoendocrine imbalance, such as behavioral and endocrine changes, which may be relevant for pathogenetic and/or pathophysiological mechanisms underlying disease progression [34]. In particular, Pérez., *et al.* [34] detected parasite or parasite genes and antigens in the HPA axis, accompanied by the presence of inflammatory infiltrates with both T lymphocytes and macrophages, and an enhanced extracellular matrix (ECM) deposition. As regards the GC function, others and we reported a rise in serum GC levels, in both acute and chronic phases of *T. cruzi* infection. Such adrenal response is paralleled by an important increase in TNF-α, IL-1 and IL-6 levels. Nevertheless, in these animals, a decreased content of CRH was seen in the hypothalamus, whereas the circulating levels of ACTH did not change significantly, thus indicating a disruption in the normal hormonal HPA feedback control. Considering the *in vivo* and *in vitro* studies, it is possible that IL-6 per se, is involved in the rise of GC production by the adrenals [31].

Lepleteir., *et al.* [35] evaluated the systemic and intrathymic levels of PRL and GC in acute phase mice of *T. cruzi* infection. Finding that the increase in the serum levels of GC was parallel to a decrease in the intrathymic content of corticosterone, clearly indicating that the control of the intrathymic production of GC is independent of the systemic levels of GC. Similar to data on circulating leptin levels, they

also found a decrease in the amount of PRL in the blood of infected animals. Also detected inverted kinetic changes in the serum levels of GCs and PRL of infected mice. They also studied intrathymic production of corticosterone and PRL and found that the kinetics were very different, the GC content decreased transiently in the thymus, whereas the PRL increased progressively.

Authors, also demonstrated that CD4+ CD8+ thymocytes from infected mice presented reduction of the GCR-α transcript, in parallel to an increase in PRL receptor (PRLR) gene expression, indicating that PRL counteracts the GC effects, by a cross-talk action directly affecting GR signaling in CD4+ CD8+ cells. This is in keeping with the data showing that phosphorylated STAT5 transcriptional activities elicited by signaling generated by PRLR/PRL ligation, significantly abrogate the GC-induced apoptosis in T cells [36]. In this respect, re-establishing systemic PRL level by metyrapone treatment (that stimulates PRL secretion by the pituitary gland) prevented thymic atrophy by decreasing CD4+ CD8+ apoptosis, largely decreasing the numbers of CD4+ CD8+ cells in the periphery of the immune system, thus demonstrating that PRL-mediated thymus protection also influences the abnormal export of these immature potentially autoreactive T cells.

Correa de Santana., *et al*. [31] investigated perturbations in the HPA axis of mice with acute *T. cruzi* infection and signaling molecules that could be involved in the production of ACTH *in vivo* and *in vitro*. The authors observed parasites in the adrenal gland of the infected mice, while the amplification product of the parasite's (DNAk), was found in the adrenal and pituitary glands. However, a decrease in CRH and an increase in corticosterone content were detected in the hypothalamus and serum of infected animals. In contrast, no significant changes were found in ACTH levels, whereas serum levels of the glucocorticoid stimulating cytokine (IL-6) increased compared to the control group. When they analyzed the effects of *T. cruzi* on the ACTH-producing cell line atT-20, found that cultures inoculated with the parasite had low levels of ACTH and pro-omielanocotin with respect to the control. In these cells a strong phosphorylation of STAT-3 was observed, with an increase in the synthesis of IL-6, of the suppressor of cytokine signaling 3 (SOCS-3) and of the inhibitor of the activated protein STAT3 (PIAS-3), which could explain the partial block in the production of ACTH. These findings indicate that the HPA axis is altered during acute *T. cruzi* infection, which could be due to a direct or indirect influence of the parasite on endocrine homeostasis.

In order to investigate the correlation between immunoneuroendocrine abnormalities and various clinical manifestations of Chagas disease, Pérez., *et al.* [37] evaluated the characteristics of the neuroimmunoendocrine response in patients with different degrees of chronic chagasic myocarditis. The investigators found a systemic inflammatory scenario in patients with severe myocarditis characterized by high levels of TNF-α, IL-6, IL-17, CCL-2, IFN-γ and NO in serum when compared with healthy individuals. This was accompanied by a decrease in the concentration of dehydroperasesterone sulfate (DHEA-s) and an imbalance in the cortisol/DHEA-s ratio. Given that DHEA-s is an adrenal androgen involved in immunomodulatory mechanisms, these data indicate a lack in the control of the inflammatory response that could contribute to the evolution of the pathology. The determination of the role of such neuroendocrine changes in the pathophysiology of Chagas disease is still being studied, considering the scarcity of clinical studies and the lack of strong evidence of hormonal involvement in Chagas cardiomyopathy.

Dysregulation of the HPA-axis also exacerbates the sepsis syndrome and SIRS. Lipinska-Gediga., *et al.* [38] reported that the median level of pro-atrial natriuretic peptide (pro-ANP), an ACTH inhibiting factor, was significantly higher in non survivors than in survivors with septic shock. They suggested that the plasma level of pro-ANP in these patients could be a valuable prognostic marker. Chida., *et al.* [10] have established mice having an inactive MC2R gene in order to study its roles *in vivo*. MC2R deficient mice lack the ability to produce glucocorticoids. In response to LPS, they showed increased release of inflammatory cytokines to exacerbate endotoxin-induced septic shock suggesting the important role of adrenal glucocorticoid release for immunosuppression [39].

In contrast, the central nervous system (CNS) is also modulated by excessive release of pro-inflammatory cytokines, reactive oxygen and nitrogen species in the circulation and hypotension, associated with inflammation [40]. Macrophages at the site of infection are important for the initiation of the acute phase reaction of the innate immune system that activates the HPA-axis in patients with sepsis. Circulating pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, stimulate the secretion of CRF and/or arginine vasopressin to release glucocorticoids. Thus, the release of glucocorticoids in response to peripheral inflammatory stress might be attributed to the ability of immune cells to produce various cytokines. The cross-talk between the peripheral immune system and the CNS via cytokines has important implications for modulation of host defense systems in stress condition [41,42].

IFN-γ is an important endogenous regulator of the immune response. In bacterial infections, IFN-γ primes mononuclear phagocytes for phagocytosis and production of inflammatory cytokines promoting pathogen clearance [43]. These inflammatory processes tightly regulated, and uncontrolled inflammation can induce clinical complications, such as septic shock. In particular, a process of tolerance to endotoxins has an important role for protecting the host against bacteria-induced shock [44]. This phenomenon is observed when exposure to low doses of endotoxins such as LPS, a major component of inflammation produced by gram-negative bacteria, reprograms the innate immune system, which becomes transiently more tolerant to subsequent high-dose endotoxin challenges. In experimental models of endotoxin tolerance, myeloid cells have been shown to switch to an anti-inflammatory phenotype [45,46].

Using a genetic mouse model in which the gene encoding the GR is selectively deleted in NKp46+ innate lymphoid cells (ILCs), Quatrini., *et al.* [47]; demonstrated a major role for the HPA pathway in host resistance to endotoxin-induced septic shock. GR expression in group 1 ILCs is required to limit their IFN-γ production, thereby allowing the development of IL-10 dependent tolerance to endotoxin. These findings suggest that neuroendocrine axis are crucial for tolerization of the innate immune system to microbial endotoxin exposure through direct corticosterone mediated effects on NKp46-expressing innate cells, revealing a novel strategy of host protection from immunopathology.

Conclusions

The immune system represents a means of receiving information from non-cognitive stimuli that appear in the organism (infections, malignant or foreign cells) and responds to them, communicating said information (through the cytokines it produces) to the neuroendocrine system. On the other hand, the neuroendocrine system is a receptor of cognitive stimuli (light, sound, stress situation, etc.) to which it responds and its mediators (neurotransmitters and hormones) reach the immune system. Thus, there is a neuroimmunoendocrine system that allows the maintenance of body homeostasis and, therefore, the health of individuals.

In the last decade, great knowledge has been acquired about the molecular signals that orchestrate an integrated immune response and has allowed us to focus on the investigation of systemic mediators that drive and control an efficient protective response, as well as alterations in signaling and dysfunctions of the control pathway that may be involved in susceptibility and/or persistence to a certain infection.

The elucidation of the molecular mechanisms by which the hormones participate in the control or susceptibility to infections, including the interactions of the endocrine system with other systems such as the immune and nervous systems and the direct action of the hormones on *Trypanosoma cruzi*, will allow determine possible targets for the development of new drugs such as hormone analogues or strategies for controlling the immune response associated with protection.

It is evident that situations of depression, emotional stress or anxiety, are accompanied by a greater propensity to suffer from infectious processes to cancer or autoimmune diseases. On the other hand, it has been confirmed that alterations in the immune system, as can happen in an infectious process, modify the functionality of the nervous system and can reach psychotic states in some extreme situations.

Since the cells of the three systems share receptors for the mediators typical of the others, any incidence that is exerted on the immune system will affect the nervous and endocrine systems and reciprocally.

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